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The Effect of Alcohol Use on Neuroimaging Correlates of Cognitive and Emotional Processing in Human Adolescence

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Objective: This article provides an overview of the scientific literature pertaining to the effects of alcohol on neural correlates of cognitive and emotional functioning, including reward processing and cue-reactivity, in adolescence and young adulthood. ***Method:*** Peer-reviewed, original research articles that included a neuroimaging assessment of alcohol effects on subsequent cognitive or emotional processing in adolescent or young adult samples were searched (through November 2018) and summarized in the review. ***Results:*** Cross-sectional studies provided early evidence of alcohol-related differences in neural processing across a number of cognitive domains. Longitudinal studies have identified neural abnormalities that predate drinking within most domains of cognitive functioning, while a few neural alterations have been observed within the domains of visual working memory, inhibitory control, reward processing, and cue-reactivity that appear to be related to the neurotoxic effect of alcohol use during adolescence. In contrast, neural correlates of emotion functioning appear to be relatively stable to the effects of alcohol. ***Conclusions:*** Larger prospective studies are greatly needed to disentangle premorbid factors from neural consequences associated with drinking, and to detect subsets of youth who may be particularly vulnerable to alcohol's effects on cognitive and emotional functioning.

General Scientific Summary
The current body of research suggests there are a number of differences in brain markers of cognitive and emotional functioning in youth that are related to how they will use alcohol later in life. In addition, there is emerging evidence that alcohol use during the developmental period of adolescence may also impact how the brain processes cognitive stimuli. However, larger prospective research studies are needed to disentangle the effects caused by alcohol from preexisting brain differences.

Keywords: adolescence, alcohol, development, neuroimaging, fMRI

Alcohol remains the most commonly used substance throughout adolescence into young adulthood. According to the Monitoring the Future survey (2017), by 8th grade, 23% of adolescents have consumed alcohol, which jumps to 62% by 12th grade. Further, 45% of 12th graders reported having "been drunk" in their lifetime and 17% reported recent binge drinking, defined as the consumption of five or more drinks in a row at least once in the prior 2 weeks (Miech et al., 2017). The prevalence of heavy alcohol use continues to increase into young adulthood with 58% of college aged young adults (modal ages 19–22) endorsing having been drunk in the past year and 33% reporting binge drinking in the past 2 weeks (Schulenberg et al., 2018). Adolescents and young adults have an increased risk of experiencing "blackouts" and hangovers as a result of these heavy drinking episodes, as compared with adults, both of which are associated with adverse physical and psychosocial outcomes (S. K. Acheson, Stein, & Swartzwelder, 1998) and greater future alcohol problems (Courtney, Worley, Castro, & Tapert, 2018; Zeigler et al., 2005). Given the known neurotoxicity of alcohol at higher doses (for reviews see Oscar-Berman & Marinkovic, 2007; Sullivan & Pfefferbaum, 2005), understanding the consequences of alcohol consumption during the key neurodevelopmental period of adolescence is of critical importance.

Typical Structural and Functional Neurodevelopment

Adolescence is the transitional period between childhood and adulthood marked by significant structural and functional brain changes. Characteristic behavioral features, such as changes in social interactions and increases in risk-taking and experimentation, likely reflect the maturation of neuronal systems involved in the regulation of emotional and cognitive processes (Crone & Dahl, 2012; Spear, 2000).

Puberty appears to play a large role in these neurodevelopmental changes, especially with respect to the prefrontal cortex and associated executive functions (Juraska & Willing, 2017). Structurally,

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gray matter volume generally decreases after puberty (Pfefferbaum et al., 2018), likely reflecting the elimination of weak or unnecessary synaptic connections, dendrites, and/or neurons (Drzewiecki, Willing, & Juraska, 2016; Koss, Belden, Hristov, & Juraska, 2014; Willing & Juraska, 2015). Simultaneously, white matter fiber tracts continue to develop, enhancing the efficiency and speed of communication between neurons (Bava et al., 2010; Giedd, 2004; Lebel et al., 2012; Pfefferbaum et al., 2018; Simmonds, Hallquist, Asato, & Luna, 2014; Willing & Juraska, 2015). Brain maturation typically begins in lower-order sensorimotor regions, followed by regions associated with higher-order cognitive functioning (e.g., frontal-subcortical) later in adolescence, with corticolimbic systems that support the integration of executive control and emotional systems maturing in adulthood (Giedd & Rapoport, 2010; Shaw et al., 2008; Simmonds et al., 2014; Sowell et al., 2004; Stiles & Jernigan, 2010).

Structural neurodevelopmental trajectories (e.g., changes in cortical thickness, brain structural volume, and demyelination) are associated with functional cognitive and emotional development (Kharitonova, Martin, Gabrieli, & Sheridan, 2013; Nagy, Westerberg, & Klingberg, 2004; Shaw et al., 2006), with some evidence that the trajectory of change in the thickness of the cerebral cortex, rather than cortical thickness itself, is of most importance (Shaw et al., 2006). However, the relationship between structure and function is complex, with most studies finding that structural changes account for only a portion of functional development (e.g., Dumontheil, Hassan, Gilbert, & Blakemore, 2010; Olesen, Nagy, Westerberg, & Klingberg, 2003).

Functional neuroimaging methods such as functional magnetic resonance imaging (fMRI) or electroencephalography (EEG) and event-related potentials (ERPs) have also been used to measure neurodevelopment and maturational trajectories of the brain with respect to cognitive and emotional functionality. A number of detailed reviews have sought consilience in the complex literature on healthy adolescent brain development and, thus, the topic will not be covered in great detail here (e.g., Blakemore, 2012; B. Casey, Jones, & Hare, 2008; Crone & Dahl, 2012; Crone & Elzinga, 2015; Luna, Padmanabhan, & O'Hearn, 2010); however, some of the key themes are summarized below.

Resting state fMRI studies, which are devoid of any task demands, generally suggest that interactions between functional brain networks reduce with age, possibly reflecting increased efficiency in between-network communication and increased within-network communication (Blakemore, 2012). Studies assessing neural activation during task performance show a much more complicated picture across development as different brain regions develop at different rates, and some regions show increases in blood oxygen level dependent (BOLD) response to task conditions while others show decreases (Blakemore, 2012).

Regions typically recruited for basic cognitive control abilities (e.g., working memory and inhibition) in adults (such as the prefrontal and parietal cortices) appear to increase in task engagement across childhood and adolescence, although some decreases in frontal activity are observed in adolescents as compared with younger children, which may reflect increased efficiency and specialization of these nonfrontal regions (Crone & Dahl, 2012). Luna et al. (2010) suggested that the transition from adolescence to adulthood may be better reflected by a change in the "mode of operation" in performance of these basic cognitive control abilities, as opposed to focusing on specific changes within regions, citing literature that shows an initial reliance on more regionalized (e.g., prefrontal) processing in adolescence, which then shifts to a reliance on a broader network of regions in adulthood. This shift is thought to reflect an increase in flexible and efficient processing.

For tasks requiring higher cognitive abilities (e.g., decision making), children seem to recruit distinct, yet frequently larger and more diffuse prefrontal regions than do adults, with task relevant patterns of activation becoming more refined and uncorrelated task activation diminishing with age (B. Casey et al., 2008). Crone and Dahl (2012) proposed that the variability observed in neural markers of cognitive control during adolescence may reflect a greater flexibility of the frontal control network as compared with adults, which allows the adolescent to shift cognitive priorities based on social and motivational salience of the context. Further, it is difficult to disentangle whether changes observed in BOLD response reflect age-related alterations in regional brain function or differences in the use of cognitive and emotional strategies that engage disparate neural circuitries (Luna et al., 2010).

Affective processing appears to follow a nonlinear developmental pattern, where the greatest processing of both positive (e.g., rewards and happy faces) and negative (e.g., threatening) stimuli seems to peak in mid-adolescence (Crone & Dahl, 2012). However, a review of longitudinal studies on typical development suggest that patterns of activation in subcortical regions (e.g., amygdala) are more variable over time than cortical regions, perhaps reflecting the presence of a wide distribution of individual differences in affective processing despite the overall average peak in mid-adolescence (Crone & Elzinga, 2015).

In summary, the typical developmental trajectories of the neural correlates of cognition and emotion are complex and likely involve large-scale shifts in network engagement as the brain becomes more efficient with increasing age. The quality and rate of these neural changes are also undoubtedly influenced by a number of individual factors such as sex, puberty, genetics, environment (including social influences), and culture (Blakemore, 2012; Crone & Dahl, 2012). Synaptic pruning of gray matter and myelination of white matter appear to be, in-part, modulated by ones' experience, which may reflect both the ongoing plasticity (via pruning) and stabilization (via myelination) of neural systems during adolescence (Spear, 2013). Exposure to neurotoxins such as alcohol during this critical period could have a significant impact on these neurodevelopmental trajectories (Muller-Oehring et al., 2018). Studies of animal models suggest a number of alcohol-related effects on the adolescent brain, including enduring neuroinflammation, decreased formation of new brain cells (i.e., neurogenesis), changes to the activities of neurotransmitter systems in several brain regions, and alterations to gene expression via epigenetic mechanisms (for a review see Hiller-Sturmhofel & Spear, 2018). For example, decreases in neurogenesis (Ehlers, Liu, Wills, & Crews, 2013) and even cell death (Broadwater, Liu, Crews, & Spear, 2014) have been observed in the hippocampus after adolescent binge-like ethanol exposure in rats. These hippocampal alterations have been correlated with behavioral markers of hypoactivity and disinhibitory behavior up to 8 weeks after exposure (Ehlers et al., 2013). Thus, alcohol consumption during neurodevelopment may impart similar detriments to the human adolescent, potentially creating a cascade of functional consequences that persist throughout adulthood.

Aims and Methods of the Review

This review provides an overview of the literature pertaining to the effects of alcohol on neural correlates of cognitive and emotional functioning, including reward processing and cue-reactivity, in adolescence and young adulthood. Literature searches were conducted on PubMed and Google Scholar and included a combination of the search terms "adolescence" or "young adults," "fMRI" or "neuroimaging," "alcohol," and an additional term from the following: "cognition" (or related words: "working memory," "inhibitory control," "reward processing," "learning," and "cue-reactivity"), "emotion," and "affect." An effort was made to include all studies across all years (through November 2018) that included a neuroimaging assessment of alcohol effects on *subsequent* cognitive or emotional processing in adolescent or young adult samples. The studies identified were grouped based on target domain of interest and presented based on these groupings below (i.e., spatial working memory, visual working memory, contextual memory, verbal learning, inhibitory control, emotional functioning, reward processing, and cue-reactivity). Cognitive and emotional functioning, although often overlapping in terms of underlying neural network engagement, are presented as separate sections to enhance the readability of the review. The roles of family history of alcohol use disorder and level of response to alcohol will also be briefly discussed, as these factors appear to promote more problematic adolescent alcohol use outcomes. The review will conclude with a discussion of the salient themes identified in the literature, with relevant gaps highlighted as potential future directions.

Alcohol Effects on Neural Correlates of Cognitive Function

Research has investigated cognitive functioning both as a predictor and consequence of adolescent alcohol use. Poorer cognitive functioning in domains such as inhibition (Squeglia, Jacobus, Nguyen-Louie, & Tapert, 2014) and working memory (Khurana et al., 2013; Peeters, Monshouwer, Janssen, Wiers, & Vollebergh, 2014) have been shown to prospectively predict alcohol use in adolescents, whereas diminished response inhibition has been shown to predict alcohol-related problems in high risk adolescents (Nigg et al., 2006).

With respect to the cognitive consequences of alcohol use during adolescence, various measures of alcohol use during this developmental period have been prospectively associated with poorer nonverbal working memory (Peeters et al., 2014), short-term verbal memory performance (Hanson, Cummins, Tapert, & Brown, 2011), verbal memory and visuospatial performance (Nguyen-Louie et al., 2015), global verbal learning ability, verbal memory, overall word recognition discriminability, and greater reliance on recency of stimulus presentation (Nguyen-Louie et al., 2016). Notably, sex appears to moderate the effects of alcohol on cognitive functioning, such that for girls, greater drinking days over a 3-year follow-up interval predicted worse visuospatial performance at follow-up, whereas for boys, more hangover symptoms were associated with worse performance on a test of sustained attention at follow-up (Squeglia, Spadoni, Infante, Myers, & Tapert, 2009).

The experiences of alcohol-induced blackouts, alcohol hangovers, and withdrawal, as opposed to general alcohol quantity and frequency measures of consumption, are receiving increased attention as potential predictors in the adolescent literature as these postdrinking phenomena may represent more of an acute marker of neurotoxic levels of alcohol use. In line with this notion, greater hangover and withdrawal symptoms in adolescence have been found to predict worsened attention and visuospatial functioning (Squeglia et al., 2009; Tapert, Granholm, Leedy, & Brown, 2002) and poorer performance on measures of immediate and delayed recall (Mahmood, Jacobus, Bava, Scarlett, & Tapert, 2010). Cognitive differences associated with the experience of blackouts, on the other hand, appear to be driven by preexisting vulnerabilities, which may become more evident after alcohol consumption (for a review see Wetherill & Fromme, 2016).

Taken together, the longitudinal behavioral studies suggest that heavy alcohol use during adolescence is associated with various subtle yet deleterious neurocognitive deficits, which may be moderated by sex and severity of alcohol use. These results are suggestive of neurotoxic effects from alcohol consumption that, theoretically, should be detectable in functional neural markers of cognitive performance.

Neural Correlates of Spatial Working Memory

Given earlier research suggesting spatial impairments associated with alcohol dependence in adults (e.g., Brandt, Butters, Ryan, & Bayog, 1983) and in individuals with prenatal alcohol exposure (e.g., Green et al., 2009), spatial working memory (i.e., the storage and manipulation of spatial information) is a common domain of investigation in neural studies of adolescents with varying degrees of alcohol drinking histories. In one such study, male and female adolescents with a 1–2 year history of heavy drinking exhibited greater BOLD response than controls in bilateral parietal cortices, with lower response than controls in regions including the left precentral gyrus and bilateral cerebellar areas, despite the absence of behavioral differences on task performance. Within the heavy drinkers, the degree of aberration in signal was greater for adolescents who reported consuming greater amounts of alcohol in their lifetime and endorsed experiencing more withdrawal or hangover symptoms (Tapert, Schweinsburg, et al., 2004). However, females with longer drinking histories (4–5 years) have shown less BOLD response than control females in parietal and prefrontal regions of the brain during the same spatial working memory task (Tapert et al., 2001). These alcohol-dependent young women (ages 18–25) with longer drinking histories also displayed worse performance than controls on the spatial working memory trials, which was correlated with greater alcohol withdrawal symptomatology, lower spatial working memory response in the right parietal cortex, and poorer scores on neuropsychological tests of memory and cognitive flexibility.

The discrepancy observed between length of drinking histories and direction of task-related BOLD signal differences from controls, especially within parietal regions, may suggest an initial compensatory response occurring early in drinking that is overcome by alcohol interference with more severe, protracted use into young adulthood. Alternatively, sex of the study participants may partially explain this discrepancy as male and female adolescents have been shown to exhibit differential BOLD responses on spatial

working memory tasks, which were further moderated by alcohol use history. Female adolescents with alcohol use disorders showed a greater departure from control spatial working memory activation patterns than male adolescents with alcohol use disorder in frontal and temporal regions (Caldwell et al., 2005). Similarly, female binge drinkers have been shown to exhibit less activation than female controls, whereas male binge drinkers showed greater activation than male controls in bilateral frontal, anterior cingulate, temporal, and cerebellar cortices (Squeglia, Schweinsburg, Pulido, & Tapert, 2011). In this study, less activation was associated with poorer neurocognitive performance for female binge drinkers, and greater activation was associated with poorer neurocognitive performance for male binge drinkers, suggesting that females may be more vulnerable to the neurotoxic effects of heavy alcohol use during adolescence.

Co-use of multiple substances may also influence the relationship between neural correlates of spatial working memory and alcohol use. Adolescents with co-occurring alcohol and marijuana use disorder, show less inferior frontal and temporal BOLD response, but more medial frontal response, as compared with adolescents with alcohol use disorder alone, and less activation in inferior frontal and temporal regions, but more response in other prefrontal regions as compared with controls, during a spatial working memory task (Schweinsburg et al., 2005). Given the high rates of comorbid alcohol and other substance use during adolescence (Terry-McElrath & Patrick, 2018), future well-powered studies would benefit from a more detailed analysis of various combinations of substances on neurocognitive outcomes.

In summary, cross-sectional studies of adolescent drinkers consistently observe altered neural correlates of spatial working memory; however, severity of alcohol use, sex, and co-use of other substances appear to be important moderating factors that complicate the relationship. Furthermore, prospective longitudinal studies on this domain of cognitive functioning are needed to determine whether the neural differences observed function as a risk factor, or represent a consequence of alcohol use.

Neural Correlates of Visual Working Memory

Heavy alcohol use during adolescence has also been associated with altered neural correlates of visual working memory (i.e., the storage and manipulation of visual information). In a cross-sectional study, young adults with alcohol use disorder displayed less BOLD response in bilateral frontal and precentral, left superior temporal, left superior parietal, and left cerebellar cortices during a two-back task compared with a matched control group (Park et al., 2011). Similarly, binge drinking young adults showed a smaller late positive component ERP associated with hypoactivation of the right anterior prefrontal cortex during a continuous performance task (CPT), as compared with control subjects with similar behavioral performances (Crego et al., 2010). This late positive component has been related to working memory processes and prefrontal activation (Düzel et al., 2001; Schendan & Maher, 2009); thus, reduced amplitude of this component could indicate a reduction of prefrontal engagement in these young adult binge drinkers.

Yet, not all studies have found reduced engagement of prefrontal areas during visual working memory. In another cross-sectional study, young adult college students with alcoholic parents who were currently engaged in hazardous alcohol use (≥8 score on the Alcohol Use Disorders Identification Test [AUDIT]) exhibited *greater* BOLD activity of the middle frontal gyrus, in addition to reduced activation of the posterior cingulate during a two-back visual working memory task, as compared with matched students of alcoholic parents not currently engaged in hazardous alcohol use (<8 on the AUDIT) with similar task performance observed across groups (Brown-Rice et al., 2018).

Differences in direction of contrast effects across studies may be because of a number of factors such as drinking history, genetics or family history, and preexisting visual working memory abilities. Longitudinal studies may help to control for some of these factors and shed light on specific working memory pathways sensitive to the isolated effects of alcohol. In one such longitudinal study, alcohol and drug naïve adolescents were scanned before they ever used any alcohol or drugs (ages 12–16) and again approximately 3 years later (Squeglia et al., 2012). Adolescents who transitioned into heavy drinking over the follow-up period showed less BOLD response during a visual working memory task at baseline in frontal and parietal regions than matched controls, and this regional BOLD response increased after the initiation of heavy alcohol use. In addition, lower baseline BOLD response during the task predicted greater future alcohol use over and above common predictors of substance use (e.g., age, sex, and family history). These results suggest that differences in visual working memory neural response patterns are both present before the onset of alcohol use *and* further affected by subsequent alcohol use in binge drinking adolescents.

Neural Correlates of Contextual Memory

A single study was found that investigated potential alcohol-related impairments to contextual memory (i.e., the memory for details related to a particular event that often facilitate recall). In a within subjects study involving two neuroimaging measurements of contextual memory under placebo and alcohol challenge, young adults with a history of fragmentary alcohol-induced blackouts (i.e., blackouts with partial memory loss), as compared with matched controls without a blackout history, showed reduced dorsolateral prefrontal cortex and posterior parietal cortex activation while under alcohol challenge; however, no differences between the groups were observed under the placebo condition (Wetherill, Schnyer, & Fromme, 2012). These results potentially highlight specific neurobiological mechanisms associated with vulnerabilities for alcohol-related memory impairments.

Neural Correlates of Verbal Learning

As compared with working memory, less research has been conducted on alcohol's effects on neural correlates of verbal learning (i.e., the process of acquiring, retaining, and recalling of verbal material). Heavy drinking adolescents (ages 16–18) displayed significantly increased amplitudes of a recollection-related ERP component (P540, predominately left parietal), and more forgetting after a delay, as compared with substance naïve controls with similar recognition performance on a modified version of the Rey Auditory Verbal Learning Test (Smith et al., 2017). Similarly, adolescent binge drinkers (ages 16 to 18) showed greater BOLD response in right superior frontal and bilateral inferior parietal

cortices, but less response in occipital cortex during a verbal encoding task involving the learning of novel word pairs, as compared with nondrinking controls, with only marginally significant differences in word recall observed between the groups (Schweinsburg, McQueeny, Nagel, Eyler, & Tapert, 2010). A follow-up study in 16- to 18-year-olds with or without histories of binge drinking and heavy marijuana use similarly found greater BOLD response in lateral parietal and superior frontal areas, and less response in inferior frontal, medial cuneus and posterior parietal regions during the same verbal encoding task among all binge drinkers (including co-users of marijuana), as compared with nondrinking control subjects. Interestingly, adolescents who engaged in binge drinking and marijuana use evinced similar encoding-related BOLD responses to controls in frontal regions, whereas binge-drinking-only adolescents showed greater frontal BOLD response than controls, with similar task performance observed across all groups (Schweinsburg, Schweinsburg, Nagel, Eyler, & Tapert, 2011). This finding underscores the influence of substance co-use, as various substances may exaggerate, or even compensate for, alcohol's neurotoxic effects.

Together, these results suggest adolescent heavy drinking is associated with altered neural correlates of verbal encoding and recall processes, despite little effects on behavioral performance. The increase in recruitment of frontal regions in heavy drinking adolescents may reflect an alcohol-induced need for greater engagement of working memory systems to achieve similar task performance levels as controls; however, the direction of causality in this relationship remains to be confirmed.

Neural Correlates of Inhibitory Control

Diminished inhibitory control (i.e., the capacity to voluntarily regulate or inhibit prepotent behavioral or attentional responses) in adolescence is consistently implicated as a risk factor for future alcohol and substance use (for a review see B. J. Casey, 2015). fMRI studies of adolescents have identified several neural aberrations during inhibition, most commonly a reduction of frontal BOLD response, as significant predictors of greater alcohol and substance use, even in the absence of behavioral differences on the tasks (Mahmood et al., 2013; Norman et al., 2011). Cross-sectional studies of young adults also show heavy drinking related differences in neural markers of inhibition. For example, a comparison of heavy and light drinking young adults (ages 18–20) on a Go/No-go task demonstrated that heavy drinkers exhibit worse performance (increased RTs), and less BOLD response in left supplementary motor area, bilateral parietal lobule, right hippocampus, bilateral middle frontal gyrus, left superior temporal gyrus, and cingulate gyrus/anterior cingulate cortex during correct No-go trials, as compared with light drinkers (Ahmadi et al., 2013). In contrast, another study of young adults (ages 18–20) using a modified Go/No-go task with images of beer bottles serving as the No-go stimuli showed heavy drinkers exhibit worse behavioral performance (d-prime) and *greater* BOLD response in the right dorsolateral prefrontal cortex, medial frontal cortex, cingulate, and insula regions during No-go correct rejection trials, possibly reflecting increased working memory demand and control efforts (Ames, Wong, et al., 2014); however, the difference in BOLD signal contrast direction between these two studies may reflect the increased salience of the beer cues present during No-go trials of the Ames, Wong, et al. study (Ames, Wong, et al., 2014).

The cross-sectional results of the aforementioned studies may reflect preexisting differences in inhibitory functioning and do not allow for cause and effect relationships to be inferred. Acute alcohol consumption is known to affect inhibitory control processes (Gan et al., 2014; Nikolaou, Critchley, & Duka, 2013); thus, it is possible that alcohol consumption during neurodevelopment may lead to enduring effects on the neural systems responsible for successful inhibition. Consistent with this hypothesis, a longitudinal analysis of 11–16 year-olds, followed up approximately 3 years later observed that adolescents who transitioned into heavy drinking by follow-up exhibited less BOLD response during No-go versus Go trials on a Go/No-go task at baseline in frontal, parietal, subcortical, and cerebellar regions, yet increased activation after the onset of heavy drinking in frontal, parietal, and cerebellar areas, as compared with matched continuous nondrinkers who displayed decreased activation at follow-up (Wetherill, Squeglia, Yang, & Tapert, 2013). These postdrinking results imply an alcohol-related disturbance in normal neural inhibitory maturation processes in addition to a preexisting inhibitory risk profile. More important, these effects seem to appear only at heavier levels of alcohol use during adolescence, as lower-levels of use have not been shown to significantly impair maturation of inhibitory control abilities (Jurk, Mennigen, Goschke, & Smolka, 2018).

Alcohol Effects on Neural Correlates of Emotional Function

Emotion regulation abilities and the use of coping strategies in childhood and adolescence play crucial roles in the development of risk and resilience for internalizing and externalizing (e.g., alcohol use) disorders. In particular, maladaptive coping in general and the strategies of emotional avoidance, suppression, and denial have all been associated with higher levels of psychopathological symptoms in adolescents (Compas et al., 2017). Emotional processing and mood states also interact with one's ability to successfully engage inhibitory control mechanisms (Cohen-Gilbert et al., 2014; Dvorak, Pearson, Sargent, Stevenson, & Mfon, 2016). Thus, it is not surprising that impairments of emotional signal processing (e.g., recognizing facial expressions of emotion, assessment of emotion intensity, and decoding affective prosody) have been implicated in the development and maintenance of alcohol use disorders (Oscar-Berman & Bowirrat, 2005), with a number of studies showing divergent neural correlates of affective processing observed between adult alcohol use disorder cases and controls (Müller-Oehring et al., 2013; Padula, Anthenelli, Eliassen, Nelson, & Lisdahl, 2015; Schulte et al., 2017), and as a predictor of young adult problem drinking (Nikolova, Knodt, Radtke, & Hariri, 2016).

Young adult college students with alcoholic parents who were currently engaged in hazardous alcohol use reported more anxiety, depression, and posttraumatic stress symptoms and also exhibited greater activity of the left middle frontal gyrus when rating negative stimuli on valance on a ranking emotion task, as compared with matched students of alcoholic parents not currently engaged in hazardous alcohol use. Further, greater BOLD response in this region was associated with higher levels of anxiety experienced during the negative condition on the task and hazardous alcohol use (Brown-Rice et al., 2018), suggesting a functional link be-

tween altered processing of negative emotional stimuli and alcohol use. Similarly, greater alcohol use disorder symptomatology in a sample of adolescents (ages 14–16) with varying alcohol and cannabis use histories was associated with greater amygdalar BOLD response contrast during emotional (vs. neutral) stimuli on an affective Stroop task. Specifically, greater alcohol use disorder severity was associated with enhanced amygdalar response to positive affect trials in all subjects, and to negative affect trials in subjects with high comorbid cannabis use disorder symptomatology, indicating hyper-responsiveness to positive and negative affective stimuli in adolescents as a function of alcohol use disorder (Aloi et al., 2018).

The amygdala is an important region for emotion processing and is often reported to be acutely affected by alcohol consumption (Gilman, Ramchandani, Davis, Bjork, & Hommer, 2008; Gorka, Fitzgerald, King, & Phan, 2013; Sripada, Angstadt, McNamara, King, & Phan, 2011). A large cross-sectional study of adolescents under resting state conditions (i.e., involving no task demands) elucidated an effect of alcohol use history on the emotion network, with weaker amygdala connectivity to medial parietal activity observed in moderate-heavy drinking adolescents as compared with matched no-low drinkers (Muller-Oehring et al., 2018). In a baseline study of adolescents and young adults (ages 12–25), functional connectivity between the amygdala and orbitofrontal cortex during resting state was found to mediate the relationship between testosterone and alcohol use such that higher testosterone levels in boys, but not girls, were associated with less functional connectivity between the amygdala and orbitofrontal cortex. This reduced connectivity was then found to be related to increased recent (past month) and lifetime alcohol use, with the most pronounced effects observed in mid-adolescence (ages 14–16; Peters, Jolles, Van Duijvenvoorde, Crone, & Peper, 2015). Importantly, results from the follow-up time point approximately 2 years later found that amygdala-orbitofrontal functional connectivity at baseline significantly predicted alcohol use at follow-up regardless of sex, whereas the reverse relationship was not observed (Peters, Peper, Van Duijvenvoorde, Braams, & Crone, 2017), suggesting the reduced coupling of amygdala and prefrontal regions serves as a vulnerability to future alcohol use across sexes and is relatively stable to the effects of acute alcohol use.

Acute alcohol-related effects on neural processing of emotional stimuli appear to depend on preexisting personality characteristics. In a double dissociation study, 48 young adults (mean age ~20) with high anxiety sensitivity or high sensation seeking personalities completed a face emotion processing task involving the identification of emotions, and a social stress paradigm during fMRI sessions under placebo and alcohol challenge. Participants were then assessed again on alcohol and substance use 2–3 years later and classified as "transitioners" if they met two or more criteria for alcohol or substance use disorders. Acute alcohol versus placebo challenge was found to elicit differential regional BOLD responses to the emotion and stress paradigms between the personality groups in regions including the amygdala, medial orbitofrontal cortex, anterior cingulate, and nucleus accumbens. Further, high anxiety sensitivity subjects who transitioned by follow-up were found to have greater alcohol versus placebo response for threat-related amygdala activations at baseline as compared with nontransitioners; whereas high sensation seeking subjects who transitioned by follow-up showed greater alcohol versus placebo response in the medial orbitofrontal cortex during acute social stress, as compared with nontransitioners (Shakra et al., 2018). These results suggest that personality-specific regional brain activations during emotional or stress processing while under alcohol intoxication are associated with increased risk for alcohol- and substance-related problems.

Thus, the culmination of results from cross-sectional and longitudinal fMRI studies suggest aberrant neural processing of emotional stimuli, especially within the amygdala, most likely serves as a risk factor for alcohol-related outcomes in adolescence, as opposed to a consequence of alcohol use. Given the effects of acute alcohol consumption on neural processing of positive and negative stimuli (Gilman et al., 2008; Padula et al., 2011), longitudinal designs that take into account potential moderating factors such as sex, personality, and social influences (Crone & Dahl, 2012) are needed to confirm the stability of neural markers of emotional processing after heavy alcohol use in adolescence.

Alcohol Effects on Neural Correlates of Reward Processing and Cue-Reactivity

The construct of reward processing incorporates facets of cognitive and emotional processing that are thought to play a critical role in early alcohol use. Variations in reward evaluation may be particularly influential during adolescence given the heightened propensity toward novelty seeking and risk taking that occurs during this developmental period (Ernst, Pine, & Hardin, 2006).

Neural Correlates of Reward Processing

Analysis of the Imaging Genetics (IMAGEN) study data including healthy adolescents (age 14 at baseline) found that reward-related BOLD activation during win anticipation on the Monetary Incentive Delay (MID) task, along with personality and behavioral traits, aided in the prediction of early onset drinking in adolescents (Nees et al., 2012). Similarly, a cross-sectional study of young adults found that greater alcohol consumption, along with greater trait disinhibition and lower IQ, was associated with greater reductions in medial prefrontal cortex activity during reward-seeking behaviors, and greater increases in medial prefrontal activity during reward-seeking outcomes on the Balloon Analogue Risk Task (Bogg, Fukunaga, Finn, & Brown, 2012), possibly indexing a neural mechanism of cognitive control that varies based on these risk traits. On a task of reward-related decision-making (the Iowa Gambling Task), adolescent binge drinkers evinced worse task performance and greater BOLD response during decision-making (vs. a sensory control task) in the limbic brain regions (i.e., amygdala and insula), as compared with matched controls. Further, greater alcohol-related problems in the binge drinkers were positively related to BOLD response in the insula and negatively related to BOLD response in the orbitofrontal cortex (Xiao et al., 2013).

Only one study to date has investigated the prospective effects of alcohol use in adolescence on subsequent neural correlates of reward processing. In this study, adolescents who transitioned to binge drinking during follow-up (ages 14–18), as compared with controls, were found to exhibit reduced reward BOLD response in the left cerebellum (but not ventral striatum) at follow-up on a modified version of the Wheel of Fortune (WOF) fMRI task,

controlling for baseline visit BOLD activation. This BOLD response was negatively correlated with past 90 day alcohol consumption, suggesting a dose response relationship between cerebellar correlates of reward processing and alcohol use (Cservenka, Jones, & Nagel, 2015). In sum, although the extant literature primarily supports preexisting differences in prefrontal- and limbic-related reward processing markers as a risk of subsequent alcohol use, emerging evidence suggests there may be a bidirectional relationship in other regions where alcohol use further modifies the neural processing and evaluation of rewards.

Neural Correlates of Cue-Reactivity

Cue-reactivity (i.e., physiological and subjective responses to the presentation of specific cue stimuli) is commonly thought to represent a classically conditioned response to alcohol or drug stimuli which is, at least initially, associated with learned reward processes. It is closely tied to craving for substances as the cues are thought to elicit incentive salience through experience with repeated cue-drug pairings (Robinson & Berridge, 1993, 2001). Alcohol cues have been demonstrated to elicit craving in adolescents, both in the lab and in the natural environment, which in turn is associated with higher volumes of subsequent alcohol use. Importantly, alcohol cues appear to be stronger predictors of craving among adolescents with greater problematic drinking habits versus those with few alcohol problems (Ramirez & Miranda, 2014).

Early fMRI studies of cue reactivity in alcohol-dependent young women (ages 18–24) showed greater BOLD response during alcohol word presentation trials in prefrontal, insular, subcallosal, and anterior cingulate regions, as compared with nondependent young women. Greater alcohol craving was related to increased BOLD response in the subcallosal cortex among these young women (Tapert, Brown, Baratta, & Brown, 2004). Similarly, increased BOLD response to alcohol picture cues was observed in anterior cingulate, prefrontal and limbic brain regions in teens with alcohol use disorders (ages 14–17), as compared with demographically matched controls. In this study, greater BOLD response to alcohol cues was related to greater drinks per month, particularly in inferior frontal, dorsal cingulate, and precuneus or posterior cingulate regions (Tapert et al., 2003). Comparison of teens with and without a family history of alcohol use disorders in this study also revealed that family history affects BOLD markers of cue-reactivity in prefrontal and cingulate regions (among others), especially within teens with an alcohol use disorder (Tapert et al., 2003), suggesting that genetics or early environmental experiences may also predispose an individual to altered neural representations of cue-processing.

Subclinical heavy drinking is also associated with neural differences in cue-reactivity. In one study, 18–21-year-old heavy drinkers displayed greater BOLD response than light drinkers during alcohol cues in regions including the anterior cingulate, medial frontal cortex, dorsal striatum, and precuneus, and even greater activation to the repetition of alcohol cue images in temporoparietal, frontal, and insular regions (Dager et al., 2013). This is consistent with the results of another study comparing heavy and light drinking young adults (ages 18–22) on neural correlates of implicit alcohol associations which showed that heavy drinkers, as compared with light drinkers, had greater activity in the anterior cingulate and insula during compatible (i.e., positive implicit associations toward alcohol) trials on the task (Ames, Grenard, et al., 2014).

Longitudinal investigations have begun to differentiate preexisting cue-reactivity profiles from the neural modulations because of alcohol exposure. In a study of young adult college students (ages 18–21) with varying drinking at baseline, the young adults who transitioned to heavy drinking during a year follow-up period displayed greater BOLD alcohol cue reactivity at baseline in caudate, frontal, cingulate, and insular regions compared with those who remained continuously moderate or continuously heavy drinkers over the period. Further, greater baseline alcohol cue-reactivity predicted larger increases in drinking and more alcohol-related problems, over and above other risk factors, such as family history of alcohol use disorders and impulsivity (Dager et al., 2014). In an additional longitudinal study, late adolescents (ages 18–19) were scanned on an alcohol cue Go/No-go task three times during their first year of college (Beltz et al., 2013). Using an effective connectivity mapping technique, the authors observed less connectivity between brain regions involved in emotion processing (e.g., orbitofrontal cortex and amygdala) when participants responded to alcohol cues versus neutral cues regardless of scan session, whereas the greatest connections in cognitive control regions were found at the second scan session corresponding to the first-semester transition into the college environment (when negative consequences of alcohol use increased), regardless of response condition (Beltz et al., 2013). Together, these results support both preexisting and postalcohol exposure changes in neural cue-reactivity profiles of heavy drinkers. Yet, despite being longitudinal in design, these studies included young adults who had already started drinking (with varying frequencies and intensities) at baseline; thus, the influence of early alcohol use on these results remains unknown.

In an attempt to capture the effects of early alcohol exposure on cue-reactivity neural profiles, a prospective longitudinal fMRI study was conducted with adolescents who were alcohol naïve at baseline (ages 12–14) and scanned again after transitioning to moderate or heavy alcohol use (ages 17–21; Nguyen-Louie et al., 2018). The results showed that, in fact, a number of risk factors influence alcohol cue-reactivity even before significant alcohol use is commenced. At baseline, (a) youth with a family history of alcohol use disorder exhibited greater BOLD response to alcohol pictures in occipital and anterior cingulate gyri as compared with youth without a family history; (b) youth with early dating experiences (i.e., before 14 years of age) also exhibited greater BOLD response to cues in anterior cingulate regions as compared with nondaters; and (c) females showed greater BOLD response than males in the left middle frontal gyrus. However, after transitioning to alcohol use at follow-up, the BOLD response patterns reversed for each factor, suggesting that the influence of each factor on neural processing of alcohol cues is dependent on personal experience with alcohol (Nguyen-Louie et al., 2018).

Taken together, these studies tend to show both preexisting and alcohol-induced aberrations of neural correlates of cue-reactivity in adolescents. Greater alcohol use appears to result in enhanced BOLD response to alcohol cues, particularly in frontal and cingulate regions. Notably, the effects of alcohol on alcohol cue-reactivity seem to abate to control levels following prolonged (28-day) abstinence in youth (Brumback et al., 2015), suggesting

that the neural alterations induced by alcohol are highly malleable, at least during the period of adolescence.

Neural Correlates of Family History of Alcohol Use Disorder and Level of Response

Family history of alcoholism is a well-established risk factor for the development of alcohol use disorders in youth (Elliott, Carey, & Bonafide, 2012; Hill & Yuan, 1999; Lieb et al., 2002). Several studies have identified differences in neural correlates of cognitive and emotion processing in adolescents with a positive family history for alcohol and substance use disorders, before the onset of personal alcohol use. Family history positive adolescents have shown altered BOLD responses during tasks involving inhibitory control (A. Acheson et al., 2014; Schweinsburg et al., 2004; Silveri, Rogowska, McCaffrey, & Yurgelun-Todd, 2011), working memory (Cservenka, Herting, & Nagel, 2012; Mackiewicz Seghete, Cservenka, Herting, & Nagel, 2013; Spadoni, Norman, Schweinsburg, & Tapert, 2008; Wetherill et al., 2012), and reward processing (Cservenka & Nagel, 2012; Stice & Yokum, 2014; Weiland et al., 2013; Yau et al., 2012); however, see Bjork, Knutson, & Hommer [2008] for null results), cue-reactivity (Dager et al., 2013), and facial emotion processing (Cservenka, Fair, & Nagel, 2014; Hulvershorn et al., 2013; Peraza, Cservenka, Herting, & Nagel, 2015), with varying directions of effects observed within domain, across studies, and across regions. Further, family history-related altered fronto-cerebellar functional connectivity has been observed across tasks of inhibition, emotion processing, and reward-decision making (Herting, Fair, & Nagel, 2011), suggesting family history may be more related to intrinsic circuity of higher order association cortices as opposed to altered task-specific activity (Holla, Bharath, Venkatasubramanian, & Benegal, 2018). Although the precise roles of genetics versus early environmental experiences are inherently conflated within family history investigations, emerging reports from large consortium studies suggest that personality traits and associated environmental factors are especially important determinants for the initiation of alcohol use, whereas genetic factors (e.g., genetic variations in ANKK1 and HOMER1) may be particularly influential in predicting the increase in alcohol consumption and alcohol misuse later on in adolescence (Heinrich et al., 2016). In addition, moderators, such as the propensity for externalizing behavior, may mask potential gene influences on alcohol use outcomes, similar to that of attention-deficit-hyperactivity disorder (Millenet et al., 2018), making the identification of specific gene variants involved in alcohol-related risk outcomes difficult to identify.

Similarly, individual variations in how an individual responds to alcohol have proven to be clinically important and reliable risk factors for alcohol use disorder development (King, McNamara, Hasin, & Cao, 2014; Schuckit et al., 2007) and, thus, have received increased attention in adolescent and young adult populations. In particular, the low level of response (low LR) phenotype has been shown to be a genetically influenced characteristic (Schuckit, 2009) that predicts future heavy drinking and risk for developing alcohol use disorders (Chung & Martin, 2009).

A number of studies in college-aged young adults have shown LR-related differences in neural correlates of cognitive and emotional processing with a primary finding that despite similar task-related behavioral performance, low LR individuals, meaning they need higher blood alcohol concentrations (BACs) to experience alcohol effects, tend to have greater BOLD response under baseline or placebo conditions as compared with high LR individuals (Schuckit et al., 2012; Tapert, Pulido, Paulus, Schuckit, & Burke, 2004; Trim et al., 2010). These results reflect that individuals with a low LR may exert greater cognitive effort to recognize relatively subtle differences across stimuli (Paulus et al., 2012). In adolescents (ages 15–17) with a variety of alcohol use histories, BOLD response to a visual working memory task predicted LR to alcohol (Tapert, Pulido, et al., 2004). In several regions (e.g., right frontal gyrus, bilateral temporal gyri, and right insula), increased BOLD response was related to the low LR profile, whereas other regions (e.g., right precentral gyrus, left frontal gyrus, and left parietal lobule) showed the reverse with increased BOLD response relating to the high LR profile. Thus, the relationship between LR and BOLD markers of cognitive processing appears to be region specific and task dependent. Notably, LR-related BOLD response in the right middle frontal gyrus and the left anterior insula during an emotion processing task in young adults was found to predict future alcohol consumption and alcohol-related problems at 5 year follow-up (Schuckit et al., 2016), suggesting variation in low LR neural profile is a clinically meaningful predictor of future alcohol outcomes.

Further, low LR individuals show a general tendency for dampened or attenuated BOLD response after acute alcohol administration, as compared with high LR individuals who often show the opposite response postalcohol (Paulus et al., 2012; Schuckit et al., 2012), possibly reflecting the need for greater cognitive resources in *high* LR individuals during alcohol challenge. Similarly, acute alcohol challenge studies suggest that family history (Quinn & Fromme, 2011) and certain gene variants (Hendershot, Wardell, McPhee, & Ramchandani, 2017) may predispose young adults to differential alcohol effects including high BACs and subjective intoxication. Thus, it is possible that genetics and family history of alcohol use disorders may predispose an adolescent to greater alcohol-related neural alterations once heavy drinking is initiated (Courtney et al., 2018).

Summary and Future Directions

Despite significant gaps in the literature, a few general findings can be surmised regarding the effects of alcohol on neural correlates of cognitive and emotional processing in adolescence (see Figure 1). Cross-sectional studies suggest the presence of alcohol related differences in neural processing within most cognitive domains, with longitudinal support for alcohol-related influences to neural responses of visual working memory and inhibitory control processes. Interestingly, in longitudinal studies on both working memory and inhibitory control, heavy alcohol using youth, as compared with controls, were found to exhibit less fronto-parietal BOLD response during task performance before the onset of drinking, which then increased to meet or surpass continuous nondrinkers' level after transitioning to heavy alcohol use (Squeglia et al., 2012; Wetherill et al., 2013). Longitudinal studies also provide evidence of adolescent drinking-related reductions in cerebellar BOLD response during reward processing (Cservenka et al., 2015), and some support for enhanced recruitment of cognitive control regions during cue-reactivity (Beltz et al., 2013); however, the nature of alcohol-related cue-reactivity effects appear to be

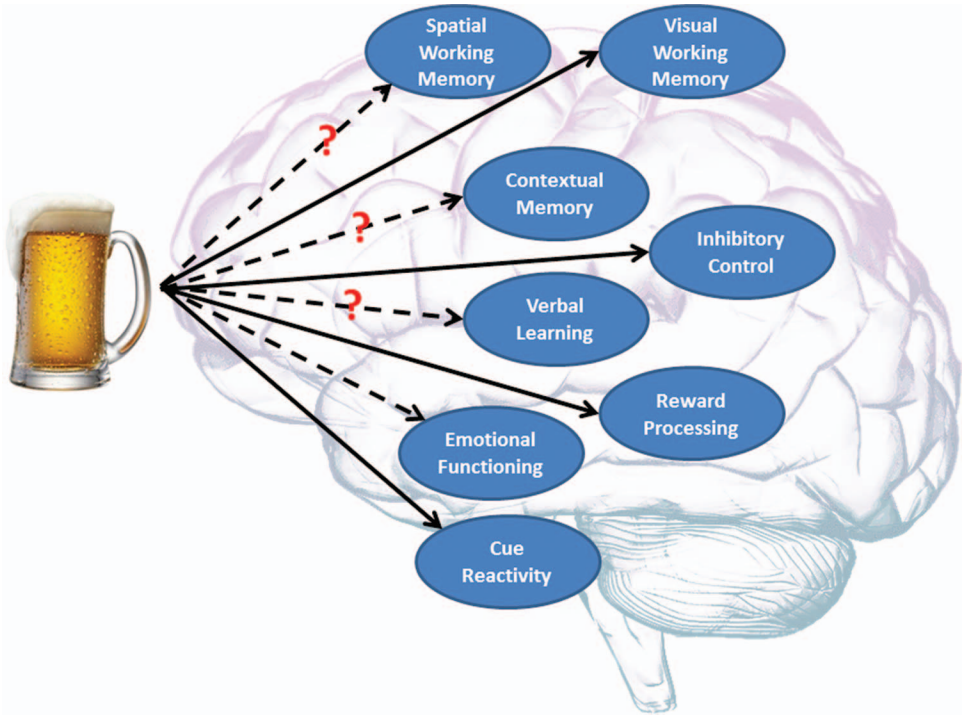

Figure 1. Model depicting the current strength of the evidence for alcohol-related effects on domains of cognitive and emotional functioning in adolescence as demonstrated by functional neuroimaging studies. Solid lines represent the presence of evidence for alcohol-related alterations of functioning, dashed lines represent the absence of any such evidence, and "?" represents domains with limited research on the topic. See the online article for the color version of this figure.

highly dependent on preexisting risk factors (Nguyen-Louie et al., 2018). These alcohol-induced neural alterations in cognitive, reward, and cue processing are most commonly observed in the absence of task-related performance differences, suggesting that either the alcohol-related effects are too subtle to cause alterations in behavioral performance or that the BOLD differences observed represent reorganizations of functional networks that allow the adolescent to compensate for the alcohol-related neural impairments. Thus, the observed BOLD differences may represent amplified changes to neural systems within the already flexible adolescent brain (Crone & Dahl, 2012).

Rodent models of alcohol use during adolescence have illuminated possible neurobiological avenues of alcohol's effects on cognitive functioning. Adolescent binge ethanol exposure in rats showed persistent inhibition of neurogenesis in the hippocampus, possibly because of alcohol-induced neuroimmune mechanisms (Vetreno & Crews, 2015). Whether this is occurring in human adolescents remains unknown; however, the one study that has directly assessed the effect of extended alcohol abstinence in fMRI profiles of human adolescents has shown recovery of BOLD response patterns to alcohol cues after 28-days of sobriety (Brumback et al., 2015), suggesting at least some of the alcohol-induced changes in neural processing are reversible with time.

Preexisting differences in neural correlates of cognitive processes are also observed in adolescents across most cognitive domains, before the onset of significant alcohol use. Factors such as sex, stage of development (e.g., puberty), genetics and family history for alcohol and substance use disorders, co-use of other substances, and social functioning appear to interact with alcohol consumption such that the specific alcohol-related neurocognitive effects an individual experiences depends on their preexisting neural profiles. The role of social factors as a predictor, and possibly a consequence of alcohol-related neurocognitive effects is especially intriguing and understudied as social functioning is critical to healthy adolescent neurodevelopment (Crone & Dahl, 2012) and is also highly intertwined with adolescent alcohol use (Bradizza, Reifman, & Barnes, 1999; Kuntsche, Knibbe, Gmel, & Engels, 2005). Furthermore, adolescents who engage in heavier drinking patterns (e.g., binge drinking) or have withdrawal and hangover symptoms tend to show the greatest deviations in neural correlates of functioning from nondrinking youth. Thus, future studies may benefit from more in-depth characterizations of these preexisting factors as well as dose-response relationships in order to identify the specific neural consequences of heavy alcohol use.

In contrast to cognitive functioning, aberrant emotional functioning in adolescent drinkers (especially with respect to facial emotion processing) appears to serve primarily as a risk factor for alcohol use in adolescence (e.g., Nikolova et al., 2016). However, there are too few studies conducted in this area to rule out the possibility of alcohol-induced consequences. Prospective longitudinal fMRI studies involving tasks that tap into various aspects of emotion processing are greatly needed to confirm the stability of emotional networks in the context of adolescent alcohol use.

In conclusion, the prevalence of alcohol use during the key neurodevelopmental period of adolescence is significant, with almost half of the youth reporting being drunk by 12th grade. Thus, it is crucial for research to uncover the impact of alcohol, or lack thereof, on the developing brain. Fortunately, the field has already recognized the need for larger, prospective studies on this important topic. Multisite neuroimaging investigations such as the Adolescent Brain Cognitive Development (ABCD) and the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) studies, which are currently underway, may help disentangle the complex causal relationships between preexisting factors and alcohol-induced neurotoxicity during neurodevelopment. A greater understanding of these relationships could help bridge the gap between neuroscience and clinical applications by informing prevention and early intervention efforts aimed at reducing detrimental alcohol-related outcomes.

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